REMARKS

Claims 58-80, 82-89, and 91-132 are pending. In the Office Action dated February 4, 2004, the Examiner rejected claims 58-61, 63-70, 72-79, 82-87, 91-123, 125, and 127-132; allowed claims 88 and 89; and objected to claims 62, 71, and 80. The Examiner also reiterated the requirement for corrected drawings as set forth in the Form PTO 948 mailed with the Office Action of May 19, 2003.[1] Finally, the Examiner withdrew clams 124 and 126 from consideration as being directed to a non-elected invention, and stated that claim 123 would be examined to the extent that it read on the elected and examined invention.

Applicants have herein amended claim 123 to reflect increases in the recited phenotypic traits, and have cancelled claims 124 and 126. Applicants respectfully assert that amended claim 123 reads on the elected and examined invention. Applicants also submit formal replacement drawings for FIGs. 1-12, and apologize for the inadvertent failure to provide corrected replacement drawings with the prior response. Applicants have amended the specification to conform the specification to the drawings. No new matter has been added. Accordingly, claims 58-80, 82-89, 91-123, 125, and 127-132 are pending.

In light of the amendments and the remarks below, Applicants respectfully request reconsideration and allowance of the pending claims.

Rejections under 35 U.S.C. § 112, first paragraph (written description)

The Examiner rejected claims 58-61, 63-70, 72-79, 82-87, 91-123, 125, and 127-132 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement for the reasons of record stated in the previous Office Action. In particular, the Examiner stated that "wide variation in structure is expected among the species of polynucleotides encompassed by the claims" and that the "specification does not disclose what

[1] Applicants note that the prior Office Action was mailed June 28, 2003. Applicants remind the Examiner that the mailing date for the Office Action was re-set from May 19, 2003 to June 28, 2003 due to the change in power of attorney in this case. Applicants have therefore assumed that the Examiner is referring to the June 28, 2003 Office Action throughout this response.

amino acids of SEQ ID NO:2 can be altered such that the resultant amino acid sequences have at least 43% identity with SEQ ID NO:2 and 60% identity to domains A and B of SEQ ID NO:2 and retain their functional activity." The Examiner went on to state that the recited various percentages of sequence identity to SEQ ID NO:2 do not describe the amino acid sequences themselves; that the description of four characteristic domains of P450 proteins does not identify a protein as having the 22α-hydroxylase activity of the claims; and that the P450 classification system based on sequence identity was arbitrarily made. Finally, the Examiner asserted that there was no written description support for the recitations "60% or greater sequence identity to domain A (or B) of SEQ ID NO:2," or the ranges of percent sequence identities to domain A or B recited in claims 127-132.

Applicants respectfully disagree. With respect to the application of the written description requirement in the biotechnology context, the Federal Circuit has held that:

> the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'

Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964 (Fed. Cir. 2002).

Independent claims 58, 76, and 86 recite polynucleotides, transgenic plants, and methods, respectively, comprising a nucleic acid encoding a polypeptide having greater than 43% sequence identity to the amino acid sequence set forth in SEQ ID NO: 2, 60% or greater sequence identity to domain A of SEQ ID NO:2, 60% or greater sequence identity to domain B of SEQ ID NO:2, where the polypeptide is effective for catalyzing the hydroxylation of campestanol. Similarly, independent claims 67, 85, and 87 recite polynucleotides, transgenic plants, and methods, respectively, comprising a nucleic acid encoding a polypeptide having greater than 43% sequence identity to the amino acid sequence set forth in SEQ ID NO: 2, 60% or greater sequence identity to domain A of SEQ ID NO:2, 60% or greater sequence identity to domain B of SEQ ID NO:2, where the polypeptide is effective for catalyzing the hydroxylation of 6-oxocampestanol. The present claims therefore expressly recite a particular function: that the

encoded polypeptides be effective for catalyzing either the hydroxylation of campestanol (claims 58, 76, and 86) or the hydroxylation of 6-oxo-campestanol (claims 67, 85, and 87). In addition, the claims expressly recite particular structures: that the polypeptides have more than 43% identity to the amino acid sequence set forth in SEQ ID NO:2, 60% or greater sequence identity to domain A of SEQ ID NO:2, and 60% or greater sequence identity to domain B of SEQ ID NO:2. Thus, Applicants have claimed polynucleotides encoding polypeptides having a combination of specific functional and structural characteristics, as endorsed by the Enzo holding.

One having ordinary skill in the art would have recognized that, at the time the application was filed, Applicants had possession of and had invented the full scope of the claimed invention. With respect to structure, the specification language provides clear support for the recited language of "60% or greater sequence identity to domains A (and B) of SEQ ID NO:2." For example, the specification states on page 18 that polynucleotides or polypeptides of the invention can demonstrate various percentage ranges of sequence identity, including 43%-60%, 60%-70%, 70-85%, 85-90%, 90-95%, and 95-98% sequence identity. Thus, the listed ranges particularly identify the number "60%," and include all values in the range from 60%-98% - all of which are "60% or greater." Page 42, lines 26-29 also lists similar ranges of sequence identity, and particularly calls out 95%, 96%, 97%, 98%, and 99% sequence identity. The percent sequence identity limitations to domains A and B in the dependent claims find similar support in the same two passages.

Further, the specification explicitly states that these various sequence identity values can be "over a defined length of the molecules." One having ordinary skill in the art would have recognized that a "defined length of a molecule" would include domains of DWF4 polypeptides, which were clearly described in the specification in numerous locations. For example, page 42 notes that a DWF4 analog can be a derivative, fragment, or fusion of native DWF4 polypeptides, and that derivatives can include changes within the domains of a DWF4 polypeptide. Example 3 describes in detail the four characteristic domains of P450 proteins. Page 53 notes that domain A binds substrate (e.g., enzymatic substrate) and molecular oxygen, while domain B is known as

the steroid binding domain. Figures 2B, 3A, and 3B then set forth the relative positions (and sequences) of these domains for the DWF4 polypeptide and other P450 proteins. Given all of the above, one having ordinary skill in the art would have thus recognized that a "defined length of a molecule" would include the described domains of the DWF4 polypeptides, including in particular domains A and B.

Applicants respectfully note that *ipsis verbis* support for claim language is not required; see Fujikawa v. Wattanasin 93 F.3d 1559 (Fed. Cir. 1996). Rather, "[i]f a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention . . . even if [not] every nuance of the claims is explicitly described in the specification, then the adequate written description requirement is met." See In re Alton, 76 F.3d 1168 (Fed. Cir. 1996). Indeed, the Applicants' brevity of language should not be held against them. Rather than mechanically repeating the various percent sequence identities that are possible at every discussion of fragments, domains, analogs, derivatives, etc. throughout the text, Applicants here placed the information in a definitional, prefatory section of the application. As the Federal Circuit has said, "[c]ertainly no length requirement exists for a disclosure to adequately describe an invention. . . . [T]he adequacy of the description . . . depends on its content in relation to the particular invention, not its length." See In re Hayes Microcomputer Products, Inc. Patent Litigation (Ven Tel, Inc. v. Hayes Microcomputer Products, Inc.), 982 F.2d 1527 (Fed. Cir. 1992). Accordingly, as the standard for written description is assessed from the viewpoint of one having ordinary skill in the art, the percent sequence identity recitations to domains A and B have more than adequate written description in the specification as filed.

With respect to the Examiner's assertions that the specification does not describe amino acid sequences themselves that would result in retained functional activity, Applicants respectfully disagree. Page 25, line 18 – page 26, line 7 notes that DWF4 analogs refer to compounds "having a native polypeptide sequence and structure with one or more amino acid additions, substitutions (generally conservative in nature) and/or deletions, relative to the native molecule, so long as the modifications do not destroy the desired activity. . . . Particularly preferred analogs include substitutions that are conservative in nature, i.e., those substitutions

that take place within a family of amino acids that are related in their side chains." The specification then goes on to point out particular replacements that may not have a major effect on desired biological activity, including leucine with isoleucine or valine; aspartate with glutamate; and threonine with serine. The specification sets forth on pages 17-18 methods for determining percentage of sequence identity over defined lengths of molecules, e.g., domains, as discussed above. Finally, Applicants note that the recited functional activity is an explicit feature of the claims. Thus, those substitutions that result in polypeptides that do not retain the recited functional activity are not within the scope of the claims. Accordingly, Applicants respectfully assert that the specification does describe amino acid substitutions that could result in retained functional activity with the resultant amino acid sequences having at least 43% identity with SEQ ID NO:2 and 60% identity to domains A and B of SEQ ID NO:2.

In light of all of the above, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 112, first paragraph (new matter)

The Examiner rejected claims 58-61, 63-70, 72-79, 82-87, 91-123, 125, and 127-132 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner asserted that the recitations "60% or greater sequence identity to domain A (or B) of SEQ ID NO:2" (and the various percent sequence identities to domains A and B in the dependent claims) were new matter and requested their removal from the claims.

Applicants respectfully disagree for the reasons given above. As indicated previously, the specification states that polynucleotides or polypeptides of the invention can demonstrate various percentage ranges of sequence identity, including 43%-60%, 60%-70%, 70-85%, 85-90%, 90-95%, and 95-98% sequence identity, and that this sequence identity can be "over a defined length of the molecules." The specification states that changes within the domains of a DWF4 polypeptide can be made, and such domains are described in the Examples and drawings, as discussed above. Such language provides clear support for the recited language of "60% or greater sequence identity to domains A (and B) of SEQ ID NO:2." The listed ranges particularly

identify the number "60%" and include all values in the range from 60%-98% - all of which are "60% or greater." The recited percentage ranges in the dependent claims find similar support in the same passage of the specification. As noted above, *ipsis verbis* support for claim language is not required. Accordingly, such recitations are not new matter and Applicants respectfully request withdrawal of the rejections.

Rejections under 35 U.S.C. § 112, first paragraph (enablement)

The Examiner rejected claims 58-61, 63-70, 72-79, 82-87, 91-123, 125, 127-132 under the 35 U.S.C. § 112, first paragraph enablement requirement for the reasons of record set forth in the prior Office Action. In particular, the Examiner stated that the specification does not reasonably provide enablement for polynucleotides that do not encode SEQ ID NO:2. The Examiner stated that the specification does not teach what amino acids can be changed to produce the claimed products that retain functional activity, and that undue experimentation would be required to determine which amino acid residues to change and to which amino acids to change them, to result in a protein with retained functional activity.

Applicants respectfully disagree. Enablement requires that the specification teach those in the art how to make and use the invention without 'undue experimentation.' See In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). As indicated previously, the specification provides guidance as to amino acid substitutions that could result in a polypeptide with retained functional activity. Page 25, line 18 – page 26, line 7 notes that DWF4 analogs refer to compounds "having a native polypeptide sequence and structure with one or more amino acid additions, substitutions (generally conservative in nature) and/or deletions, relative to the native molecule . . .. Particularly preferred analogs include substitutions that are conservative in nature, i.e., those substitutions that take place within a family of amino acids that are related in their side chains." The specification points out particular replacements that may not have a major effect on desired biological activity, including leucine with isoleucine or valine; aspartate with glutamate; and threonine with serine. Given the above and the guidance set forth generally in the entire specification, it would not require undue experimentation for one having ordinary skill in the art

to determine amino acid substitutions that would result in a polypeptide exhibiting the desired functional activity and falling within the recited percent sequence identity ranges. Applicants respectfully note that a blanket requirement for numerous explicit examples of sequences misplaces the focus of the enablement inquiry on the length of the disclosure rather than its substance. As the Federal Circuit has held, "[n]ot every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be." See DeGeorge v. Bernier, 768 F.2d 1318 (Fed. Cir. 1985) and cases cited therein. Indeed, "[n]othing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." See In re Wright, 999 F.2d 1557 (Fed. Cir. 1993). Accordingly, Applicants respectfully assert that the claims are enabled by the specification as filed, and request withdrawal of the rejections.

CONCLUSION

Applicants respectfully assert that the pending claims are in condition for allowance, which action is requested. The Examiner is invited to telephone the under-signed if such would expedite prosecution.

Enclosed is a $475.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: 8/4/04

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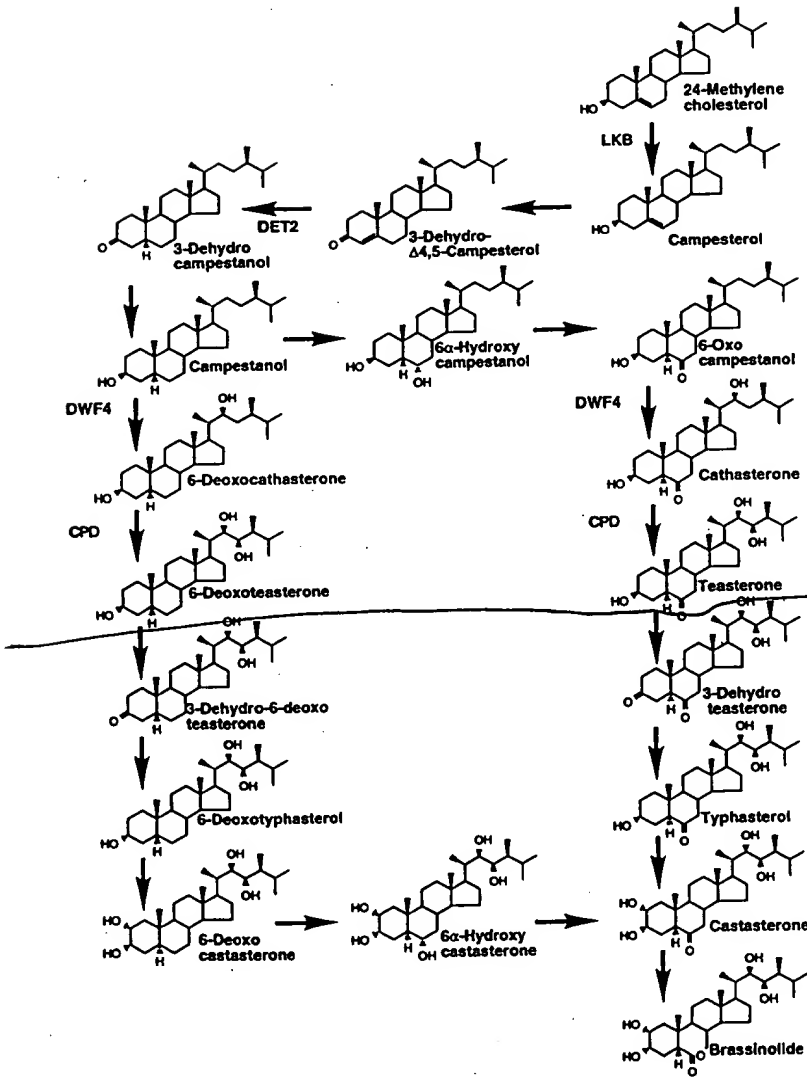


FIG. 1A

FIG. 1B

FIG. 1

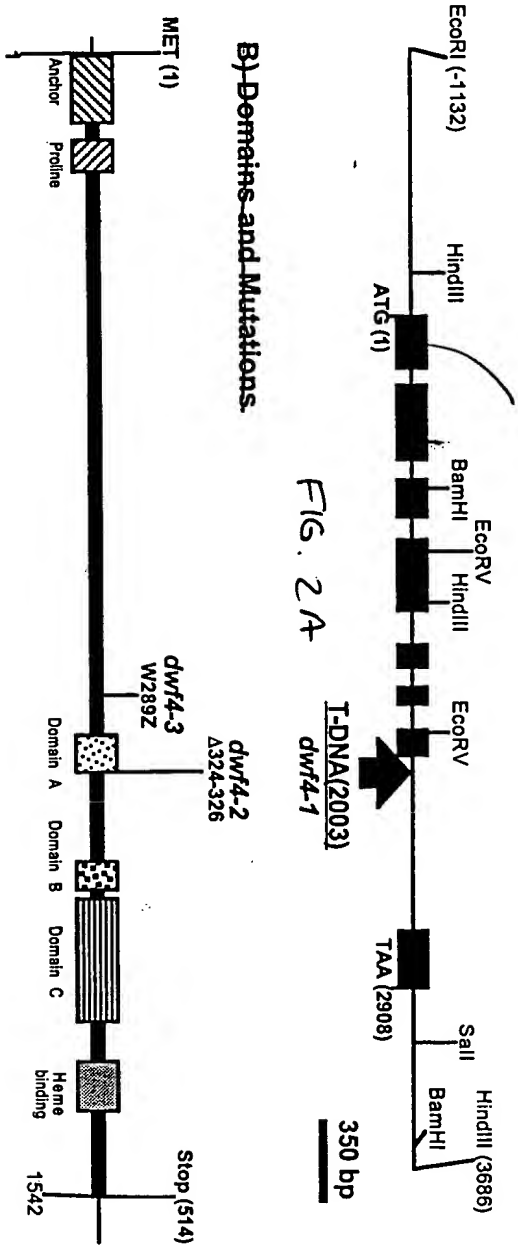


FIG. 2A

FIG. 2B

FIG. 2

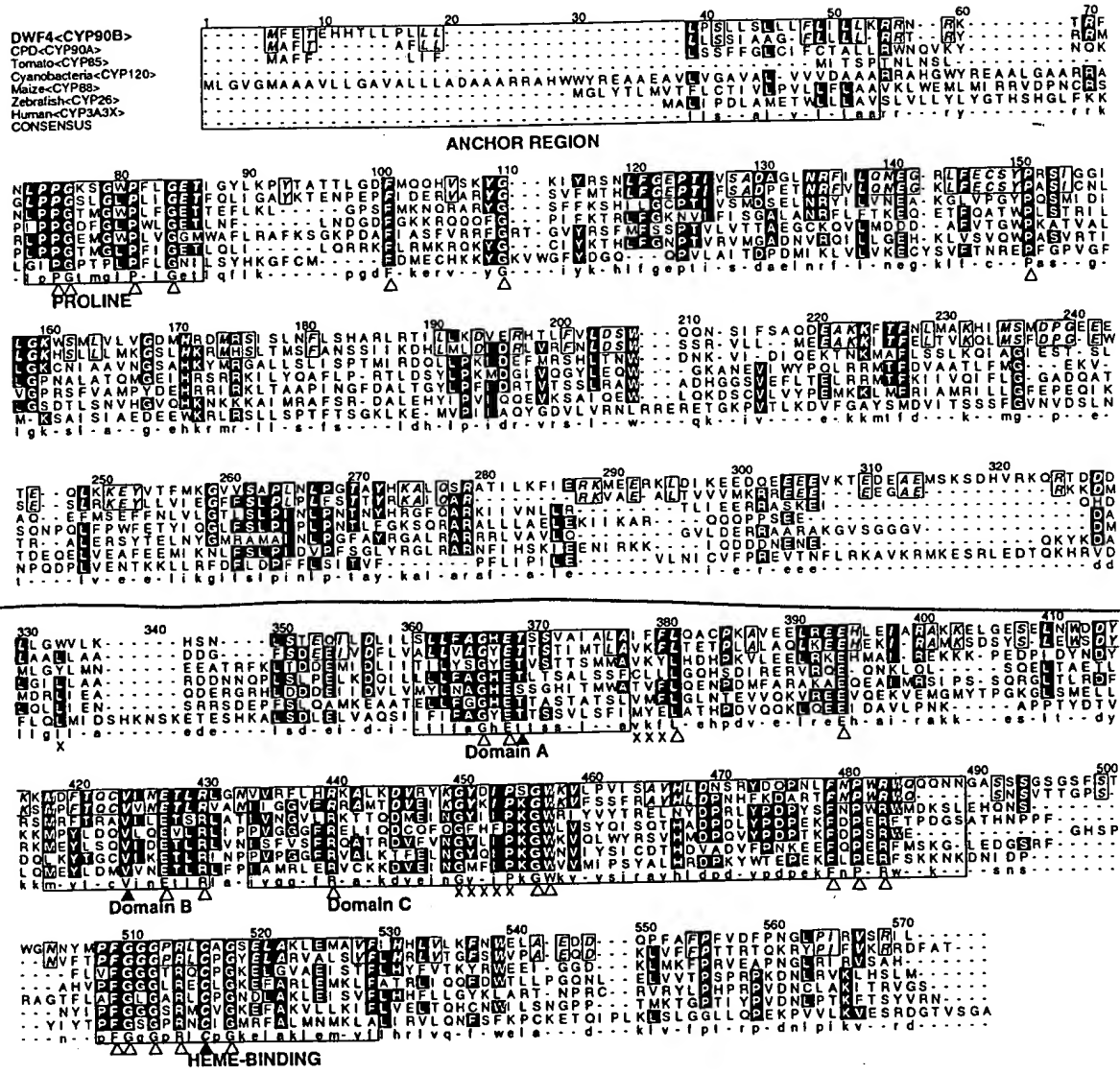


FIG. 3A

FIG. 3B

FIG. 3

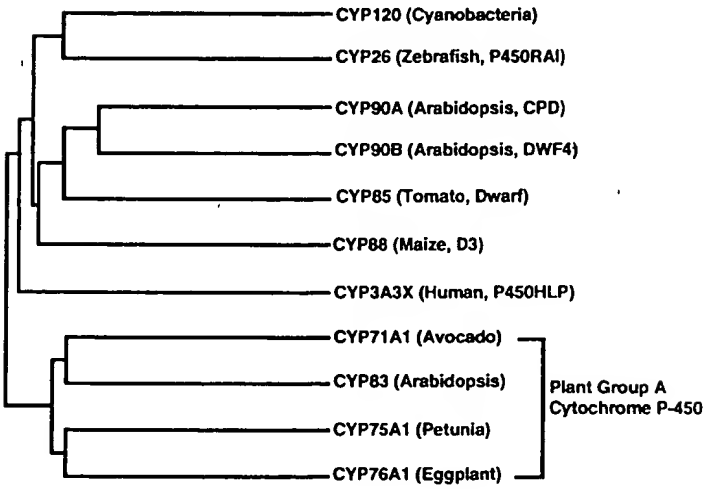


FIG. 4

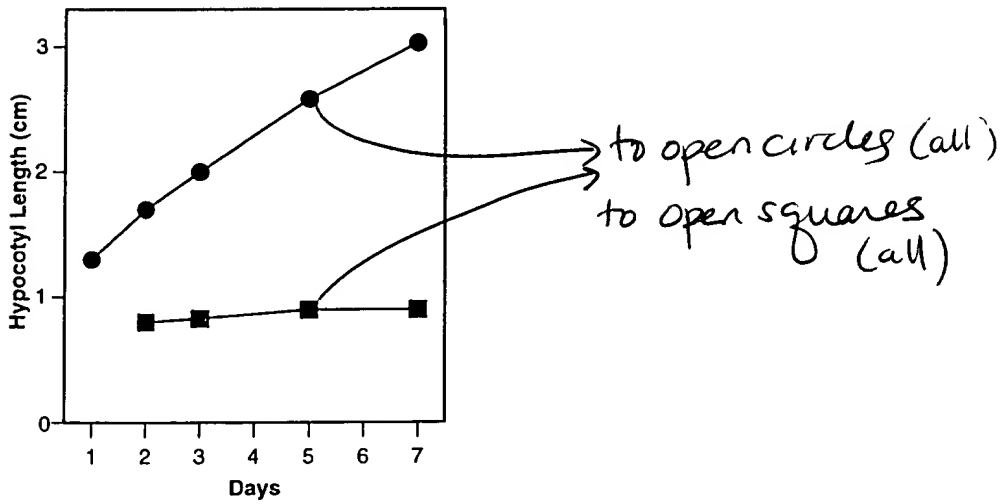
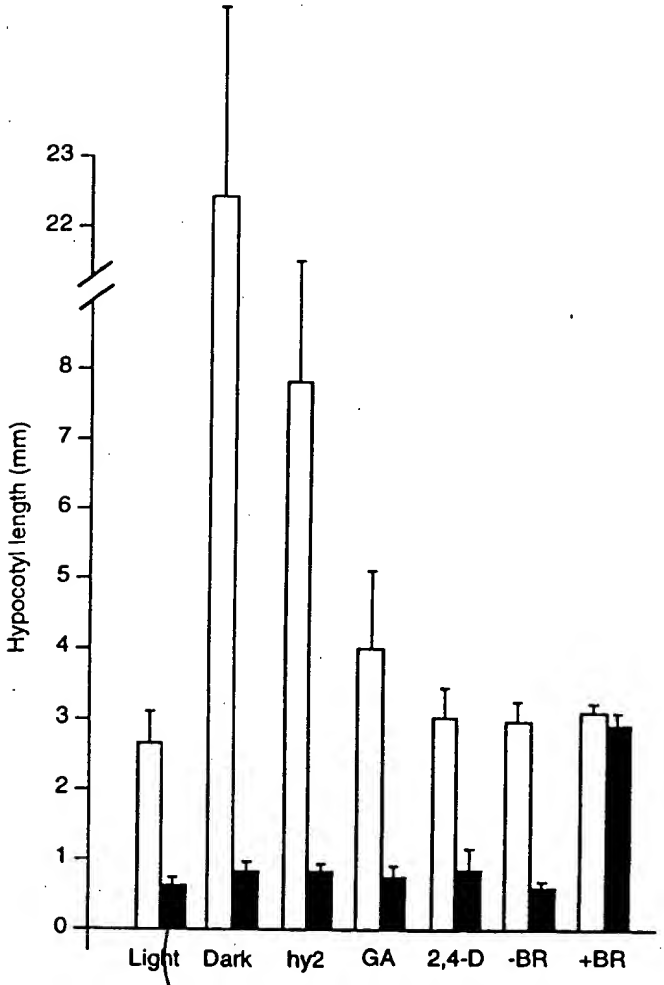
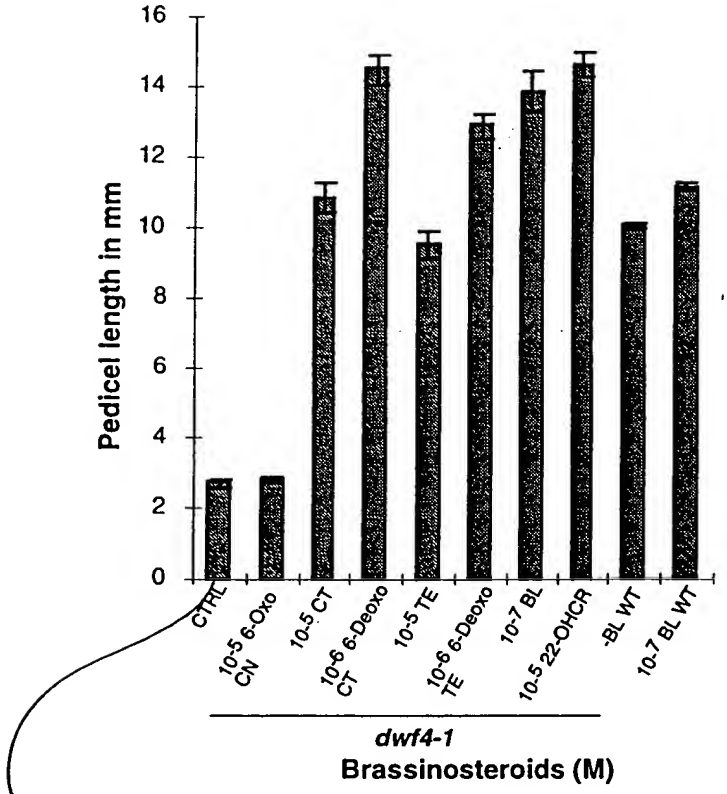


FIG. 5



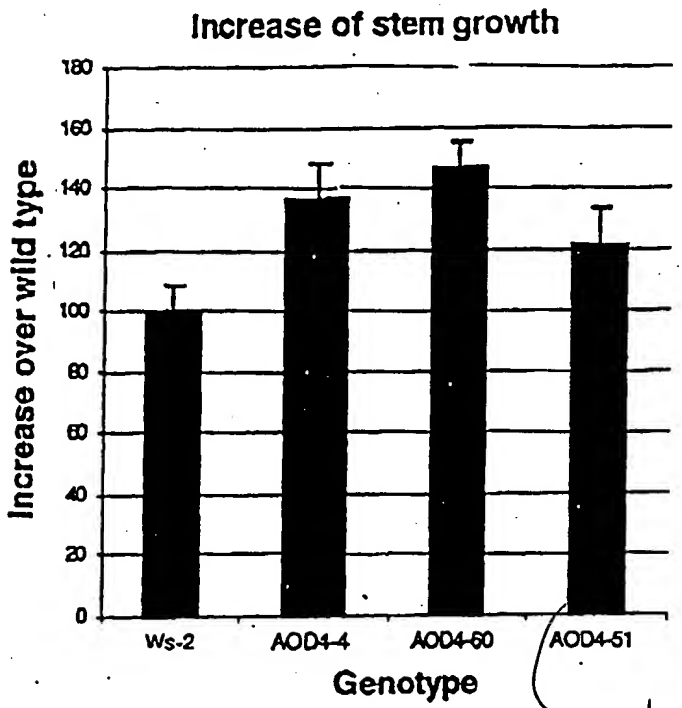
to hatched rectangles (all bold)

FIG. 6



to open rectangles (all)

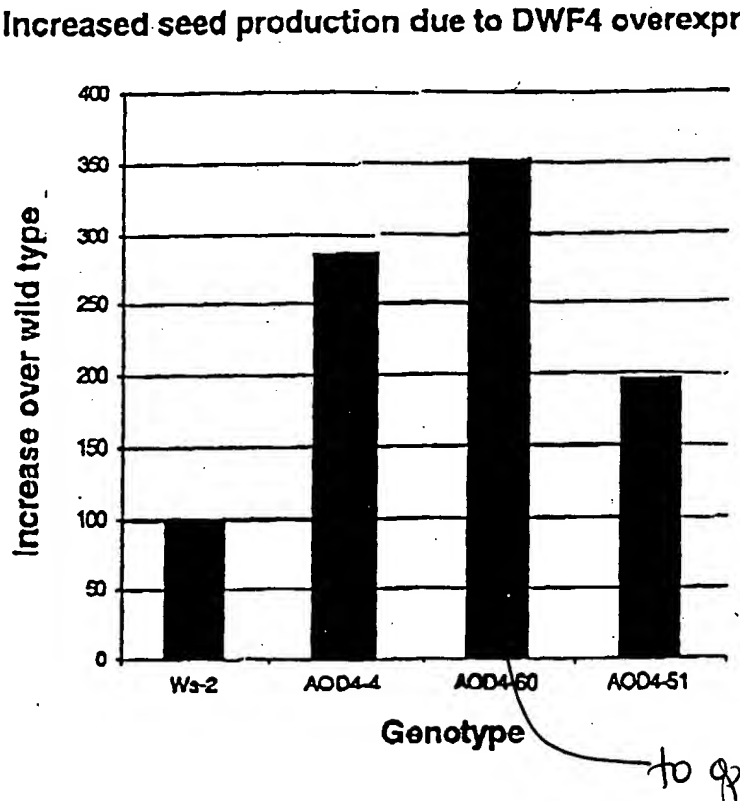
FIG. 7



to open rectangles (all)

FIG. 8

2 sheets



to open rectangles (all)

FIG. 9

1 TGTGGGTATTATATTGTTGGGTTCGGTTTGAGCTACAATATAAATTTCGTGTTTCTGGT 60

61 TATTCTGTTCACATGATTTGAGTTTGGTTCTCAATTTGGATTCCAAGATAATTAAATATT 120

121 AAAATTCATTTAAAATATTTACAAGTAATTAATTATCTTTACATTGTATTGTTATAACAA 180

181 AATATCTATCTTTGGTATATGAGAAAATATGGAGTTTGGAATTTATAATAATAAAGGAAA 240

241 TAATCGATTCCATTTGGTTGGATTACACAGTTAAGTTTTTGTGTTTCTTTTGTTATATGT 300

301 ATATGAGTAAATCAAAAAAGAGTATTGATTGAAGTGTAAACATATTTCGTTATGACCCCCA 360

361 AAAAAAAAAAAAAAAACAAACAAACAAACCCCCCCCCCCGATATAGTTTTTGGTTCTGGATT 420

421 AGGTTTATTTGATCATAATTACATGCATCATTTCTTTGATTACTATGAAGATTTTCTTAC 480

481 CAATTAAAATTTCGAATTCATATCTCTTGATTATTAAATTAAATACGAGTGTGAATATCC 540

541 GTTTATCGATCACTCCAATCATGATTATGATTCTTGTGCTAATCCAGCAAATTATTAACA 600

601 AGAGTATTGAGAAAAAACCGAAAATAAGAAAAGGGAAAGAGTAGTGACCCATGGAGTATG 660

661 TGAATAATTATCAAAGAGAATAAGAGATGACAACCAAAAGGTTGTGGAATAATGGTCCCT 720

721 GCCAGCTTTCTCTCACAATCAATATCGACCCTATTTGGATTTTCTGGATATTCGTTAAAA 780

781 TTTGCGATAACGATTGTGAAAAATATTTTATTTGTTAGCTGATCTCAATATTATGTTCCA 840

841 GGTATTTGCATAATCTTCTGTTTAAAGCATATTTTGTCTTTCTTTTTGTTTCGTTTCTCT 900

901 TAACTATATATTATCGCGGATATATGATAACAATGATATATCACAAAACAATTGTCTGGG 960

961 ACCATTTTGAATAAACTTTTTCTCAAACATTACGGGACACTGGACTCGACCCTTAAAATA 1020

FIG 10A

FIG 10A-10G expanded to FIG. 10A-10M

1021 CGATTTTACAGCGTCACTAGTTGAGATTACTAGCATAAAGCATAAAGGACCCGTTCAAGC 1080

1081 TATTTATACAAAGTTACAAACTGAATATAGCTTGAAATCCTTTAGAAAATTTTGGAATTA 1140

1141 CCGGTTGTTATGTAAATATAGATTTAGTGGTAAACAAATATGTTAATCAATTAGTGGTCA 1200

1201 ACATATACATAATTCCTTACAGAAAAAACAAACTTAAGAGAAGTTAACATATCCATATAT 1260

1261 GGGTATGCTATACCTTTCACGTATGCTATACTAGAGACTAAAGAATAGTTATGTGATGTC 1320

1321 GATAAATGAAATTCACACGCGTGGTAATAATTATGGGACCGTATGTTACGATCACTGCAA 1380

1381 ATATCATTCTTGGTTGGTCAACAATAAAAACAAAAACAAGAAAAAAAGAAAACGATTTTT 1440

1441 CTTGGATTCCATTCAATGATCTAAAATGCATAGATCTTTTGGGTTACAGTTTCGAAGTCC 1500

1501 TCTACAAGCGTGTAACCATCTGCAACTATTAAATTGCTTTCTTTAATGCATCTTTAACAT 1560

1561 ATTTATTGTTAGTTGGAATTTAATAAGAGCGAACTTGTAACATTACAATATTTATATTAG 1620

1621 ATACTAGTATGTGATTATTCCAAATACATACTTTGGATGTTTAAACTTAATCTTGTTTCT 1680

1681 TCCTACGGTATAAATATTAATCATCGAGGTAAAAAAAAGTTTTGTCTTATTTTCGCGATGC 1740

1741 ATGAAGGATAAACCTAATGACTTTAATTTTTTGAAAATGTAACCCTTTTACTCATAGATT 1800

1801 AATTACCGTATGTTTTTGTTGCCATAATGACAGCCTCTACAACTGTGATAGTCAATTTTT 1860

1861 TCTGCAAATATTAAATTAGGAATTCAATGCTACTATCAATAGAAGAAACAGCTGAGTATT 1920

1921 ACATTTTAATTTAAAGACAAAATTTTTGAAAAATGTTATAATTTCTAACAATATTATTAA 1980

1981 AATATGATGCCTATAATGTATTTCCTATGTTCTTAAAATATTTTTTTTTATATTTAGTTA 2040

2041 TAAATACATTATGAACCAATAATAGTTGGTGAATTCAAATATCTCCATTAATATTTTTTG 2100

FIG 10B

2101 AAATCTACAAATTATTAATATTTAGTCAATAACAATGCATAGAAAGTTCCAAAAAAAATT 2160

2161 TTGTTAACAGAAACTTCCAAATTTTTTTTTTTATGGAACAAGAAATAACAGATAGAAAA 2220

2221 CTATTTTGTTGTGGAATGGAAGTAGTAATATACATTAAGCAAATTTTAAAAAATTATATA 2280

2281 AGCCTATACGCGCTCAAAGTATGTTATCTAGTAGGTGTAATTAATAATGCATGGTGCGAT 2340

2341 TCAGAATTGGGACAACAATGAAAACGGAATTAAAATATTAACTTTAAAATAAATAAAAAT 2400

2401 TTGAGTAAATGTGTTTTCTGACTATTGAGGGGCAAAAAAAAAGACAATGCCAAAAGTCTAC 2460

2461 GGGTTTGACTGTCCAGTTCGGTAATAATCTAATAACTCTGTCTTTGACCGCACGCTCGTG 2520

2521 TAGGGGTCCTTCTGACATTTTCACTGTTCTACCCCTACTCGTGAGCCCACCCTTTTCCCA 2580

2581 TATCCTAAGGGTAATTTTGGAAATCCCAATTTAAACCGATTGAGACCGTACCGGACTTCC 2640

2641 TGGGATTCTGCTGGAGCATTTATCAAAAATTATTAGCACGAATGGGTTTATTAATTTAAA 2700

2701 AACTCACAACTTGATCAGATAAAATTTCATAAACACTTTTACGATGGATTCGTACGATCT 2760

2761 ATCTAATGACTTTTTTTTTTCTACCACGGTGGATGAAAGTTATAGTACTATTAGCCAGAG 2820

2821 ACAATTGATTATAGATATATCCATTAATCCATGATATTTATGATATAAATAGCTGTTAAA 2880

2881 CTATTTCAGCATCGCAGCTTTCTGCAACTTTTGTTTTTAATTTAAGAGTTTAATAAATAA 2940

2941 AAGTATTAAAAGGAGCATAACGAGGCAACAAAAGTAATGAACACGGAGAAACAAAAGCCA 3000

3001 TGAAGCTCATTGGTTAGTTTAAGCTTAATAAGAAGATTTTATTAAATTTTAATGACGATG 3060

3061 ATAACAATTATATTTTCTGACTTCTTTAAAACCCCCTCTTACAAACAGAAGCTCCCTTTT 3120

3121 TCAGTAGAAGTCCGATTCCCAATCTTAAAGACAAAGCCATTAGAAAGAGAAAGTGAGTGA 3180

FIG 10C

3181 GAGAGAGAGAGAAACTAGCTCCATGTTCGAAACAGAGCATCATACTCTCTTACCTCTTCT 3240
exon 1

3241 TCTTCTCCCATCGCTTTTGTCTCTTCTTCTCTTCTTGATTCTCTTGAAGAGAAGAAATAG 3300

3301 AAAAACCAGATTCAATCTACCTCCGGGTAAATCCGGTTGGCCATTTCTTGGTGAAACCAT 3360

3361 CGGTTATCTTAAACCGTACACCGCCACAACACTCGGTGACTTCATGCAACAACATGTCTC 3420

3421 CAAGTAAACAACAACATCTTCCAAAAACTCAAAAAAAATAAATCCTCTGTTTTTGAAATTT 3480

3481 GACTAATGTTGTTTATTTTACAGGTATGGTAAGATATATAGATCGAACTTGTTTGGAGAA 3540
exon 2

3541 CCAACGATCGTATCAGCTGATGCTGGACTTAATAGATTCATATTACAAAACGAAGGAAGG 3600

3601 CTCTTTGAATGTAGTTATCCTAGAAGTATAGGTGGGATTCTTGGGAAATGGTCGATGCTT 3660

3661 GTTCTTGTTGGTGACATGCATAGAGATATGAGAAGTATCTCGCTTAACTTCTTAAGTCAC 3720

3721 GCACGTCTTAGAACTATTCTACTTAAAGATGTTGAGAGACATACTTTGTTTGTTCTTGAT 3780

3781 TCTTGGCAACAAAACTCTATTTTCTCTGCTCAAGACGAGGCCAAAAAGGTTTTTATTTTT 3840

3841 ATCTTTTATTTTGCTAAATTTTTTTGTTTATGAATCTTTAGAGTTTCTAACTTTTTTTTT 3900

3901 TTTAATTGAACAGTTTACGTTTAATCTAATGGCGAAGCATATAATGAGTATGGATCCTGG 3960

3961 AGAAGAAGAAACAGAGCAATTAAAGAAAGAGTATGTAACTTTCATGAAAGGAGTTGTCTC 4020

4021 TGCTCCTCTAAATCTACCAGGAACTGCTTATCATAAAGCTCTTCAGGTACATTTATTTTT 4080

4081 TTTTGCTGTAAAGTCACAAACTCTCATTATAGGTTTTTAATTTTATTTTATGTGTTAAAT 4140

4141 AAAATATCTAAAATGGTTGTGTAGTCACGAGCAACGATATTGAAGTTCATTGAGAGGAAA 4200

4201 ATGGAAGAGAGAAAATTGGATATCAAGGAAGAAGATCAAGAAGAAGAAGAAGTGAAAACA 4260

FIG 10D

4261 GAGGATGAAGCAGAGATGAGTAAGAGTGATCATGTTAGGAAACAAAGAACAGACGATGAT 4320

4321 CTTTTGGGATGGGTTTTGAAACATTCGAATTTATCGACGGAGCAAATTCTCGATCTCATT 4380

4381 CTTAGTTTGTTATTTGCCGGACATGAGAcTTCTTCTGTAGCCATTGCTCTCGCTATCTTC 4440

4441 TTCTTGCAAGCTTGCCCTAAAGCCGTTGAAGAGCTTAGGGTAAGATAATTATAACAGCAC 4500

4501 AAGTTAATTACTACCAAATTGTTACGTATTATATAAGTTATTATAGAATTATTCTATTAG 4560

4561 AATATACGATGAAAAAAGTATGTATATTTAATTGTCACTAATTTTATGTTTATTGATTTA 4620

4621 TACTTTTGAAGGAAGAGCATCTTGAGATCgCGAGGGCCAAGAAGGAACTAGGAGAGTCAG 4680

4681 AATTAAATTGGGATGATTACAAGAAAATGGACTTTACTCAATGTGTATGTTACTATCATT 4740

4741 CTCATTATTTATTCTATGTTCATATGATTTATGATGAAACCAAAATTATTGATTTTTTTT 4800

4801 TTGGTGTGTGTGAAGGTTATAAATGAAACTCTTCGATTGGGAAATGTAGTTAGGTTTTTG 4860

4861 CATCGCAAAGCACTCAAAGATGTTCGGTACAAAGGTAAAACTTTACGTACAAAATTTTTA 4920

4921 AATAATGAAATCCGGAATATTGAAATCTTATTGGATGAAAAATATTAAAATAATTTACAT 4980

4981 TTCTTAATGTTGGAAAAAAGGATACGATATCCCTAGTGGGTGGAAAGTGTTACCGGTGAT 5040

5041 CTCAGCCGTACATTTGGATAATTCTCGTTATGACCAACCTAATCTCTTTAATCCTTGGAG 5100

5101 ATGGCAACAGGTAAATAAAAAGTTTCTCTCGTTAACTATCGAAAATTAGTGTATAGTTTT 5160

5161 TTCATCTATTGCATGAATAGATACGTCCTACGTGATTTACCTATCTATAGATACTATACG 5220

5221 AGAACTATTAATCTGGCAAAAACTTTTTATTATTATTATCTTTCAAGTTAGATCTTAACA 5280

5281 CGTCATGGATCATTGATCACATGAAAGCATATAAATTAAAAATAAGAGAGAGAAAGAGAC 5340

FIG 10E

5341 GTGTTGGTGTAAGTGTACGTGAAGACAATTAATTAGTAGGATGGTATGTCTTTAATGACG 5400

5401 TAGGAGCTGCCTAAATATTCTTATAATCGTGACCGTTGATTTATTATTAGTCACGGCTTT 5460

5461 GATACAATTTAAGATTTGACGGACGATGGTACCACGGCTTTGACGGATCTCACACGCCCG 5520

5521 ATGACTTGTACGTGCGTTAGATTCTGCCACGTTGACTGGTTTTAATACTTAGATTTATAA 5580

5581 CTCTATTAATTATAACAACTATCAAATCGGCGAATTAGAGAAATATACTATATAGTATTA 5640

5641 TTATGATTATTATGAGATAATACTTTATGAAATAAGATAATAATGGTAGTCATGATGTTA 5700

5701 TAGTGAGTGGGGAAGGTAAGAGGTGGTGAGAGATGATTAATGACCCCACGTGGTGTGGTG 5760

5761 CCAACAAGCACGTGTTCTTCTTCCTTTTTTCTTCCCAACTTCTTTTTTTGGGGGTTTATT 5820

5821 GTGATTTATAAAATCGGTTTGTCGTTTTTTTTTGTGACGAGCAGCAAAACAACGGAGCGT 5880

exon 8

5881 CATCGTCAGGAAGTGGTAGTTTTTCGACGTGGGGAAACAACTACATGCCGTTTGGAGGAG 5940

5941 GGCCAAGGCTATGTGCTGGTTCAGAGCTAGCCAAGTTAGAAATGGCAGTGTTTATTCATC 6000

6001 ATCTAGTTCTTAAATTCAATTGGGAATTAGCAGAAGATGATCAACCATTTGCTTTTCCTT 6060

6061 TTGTTGATTTTCCTAACGGTTTGCCTATTAGGGTTTCTCGTATTCTGTAAAAAAAAAAAA 6120

6121 AGATGAAAGTATTTTTATTCTCTTCTTTTTTTTTTGATAATTTTAAATCATTTTTTTTGC 6180

6181 CCAATGATATATAAAAATTTGGATAAATAATATTATTGGATATTCGTTTTTTAGTTCGGG 6240

6241 TTTGAGAAAAGGGTTTCGACTTTCGAAAGTGGACGATGTATATAGATTGGGAGCTAGGTT 6300

6301 GAGTCTTTGGACATTTGTATTGGATGTTGTTGATTATTAGTGTCGACACTATTAAACCTT 6360

6361 AAATGGGCTTTCTATAAGGCCCAATTATATTACGATTATAACAAAGTGACAACTTTTACT 6420

FIG 10F

6421 TCGTTTTTGATCCGAAGCAATAACAAATTGTCAAATACCAAACACAAGAATTATGTAAAC 6480

6481 ACTCGTGTGTGTCTAGTGGGAAATCATTGGGCTGGAGACTGAACATCAGAACACAAGAAA 6540

6541 CCTGTCAATTATGGATACACCTCCTATGACGGTTTCCAAACTTTATCTTGATTCTTATCG 6600

6601 TGTTACATTGACACAAAGAGTTAGGTGTCAAAAGGACTAAATGAATAACAATAGCTCTCA 6660

6661 GGATAAGAAGGTTCATAAAATGGTTTCTTTATTTTGAGAAGAAAGAGAGAGGAGCTTTTA 6720

6721 CTGTTTCTTGGGTCCTATTCCTTTAAATGAGAGGGTTTCGTTTTTACTTCTTCTATCTCA 6780

6781 TCATCTTTAGGATCCTCTTCTAGACGAGTAAAGTAATCCTCGTTACCAAGCAATGGTCTC 6840

6841 ATCTTTTGAAGACAGGTCTTTTCCAAGTCCTAGTTCAGGCCAAAGCTT 6888

FIG 10G

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  1 MFETEHHTLL PLLLLPSLLS LLLFLILLKR RNRKTRFNLP PGKSGWPFLG ETIGYLKPYT
 61 ATTLGDFMQQ HVSKYGKIYR SNLFGEPTIV SADAGLNRFI LQNEGRLFEC SYPRSIGGIL
121 GKWSMLVLVG DMHRDMRSIS LNFLSHARLR TILLKDVERH TLFVLDSWQQ NSIFSAQDEA
181 KKFTFNLMAK HIMSMDPGEE ETEQLKKEYV TFMKGVVSAP LNLPGTAYHK ALQSRATILK
241 FIERKMEERK LDIKEEDQEE EEVKTEDEAE MSKSDHVRKQ RTDDDLLGWV LKHSNLSTEQ
301 ILDLILSLLF AGHETSSVAI ALAIFFLQAC PKAVEELREE HLEIARAKKE LGESELNWDD
361 YKKMDFTQCV INETLRLGNV VRFLHRKALK DVRYKGYDIP SGWKVLPVIS AVHLDNSRYD
421 QPNLFNPWRW QQQNNGASSS GSGSFSTWGN NYMPFGGGPR LCAGSELAKL EMAVFIHHLV
481 LKFNWELAED DQPFAFPFVD FPNGLPIRVS RIL
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FIG. 11

FONT increased

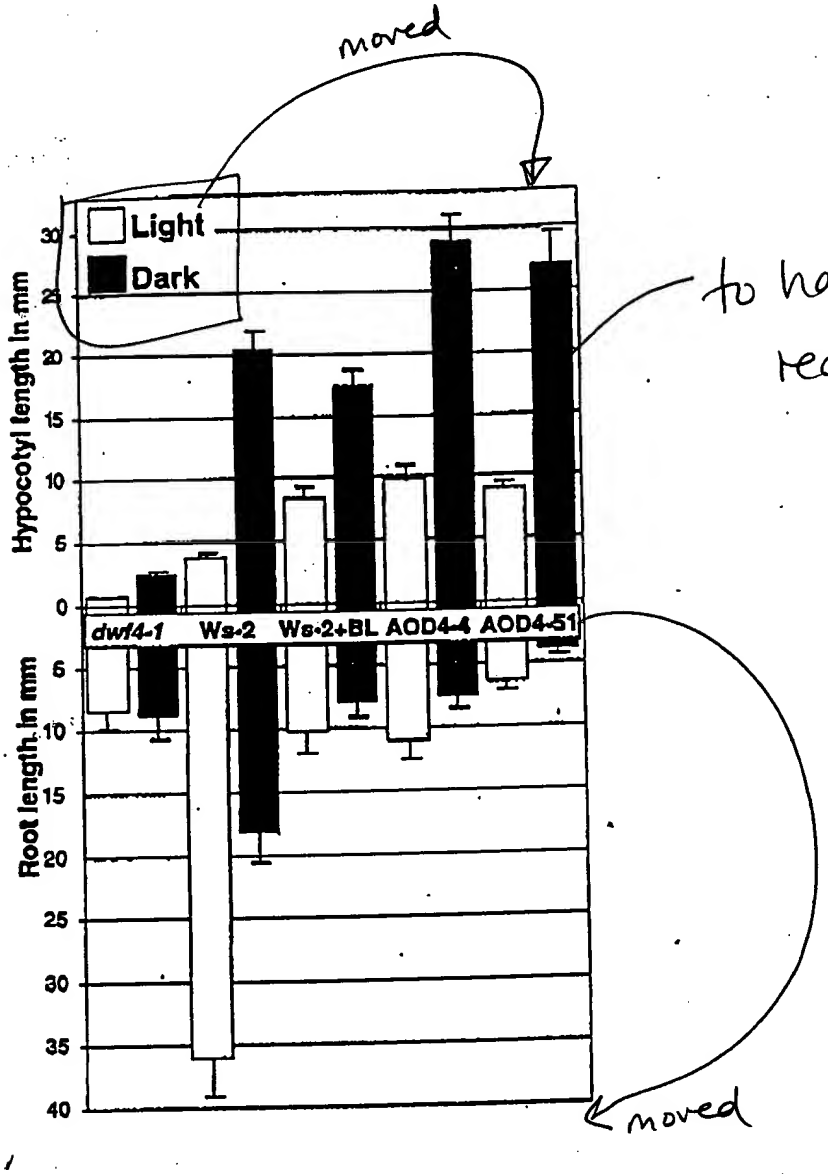

FIG. 12